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Review

Non-Hodgkin's Lymphomas—Current Status of Therapy and Future Perspectives

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Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of disorders which can either be classified according to their biology, represented by corresponding counterparts of normal lymphocyte development as in the Kiel classification, or according to their clinical course, used in the Working Formulation. The recently proposed Revised European–American Lymphoma (R.E.A.L.) classification may unify both aspects and facilitate the comparability of international studies. Besides histology, the extent of disease still comprises the major determinant of therapy. In high-grade lymphomas combination chemotherapy with cyclophosphamide, hydroxydaunorubin, vincristine and prednisone (CHOP) represents the treatment of first choice, and may be restricted to 3–4 cycles in patients with limited stages of the disease when followed by involved field radiotherapy. In more extended, bulky stage II to IV disease, treatment must be extended to six courses of CHOP and, potentially, additional irradiation. Even in advanced states of the disease, long-term remission and potential cure are achieved in 30–50% of cases. In low-grade lymphomas, most patients present with advanced stages III and IV for which chemotherapy can be applied with palliative intention only. Hence, a watch-and-wait approach still seems appropriate outside clinical investigations until the disease requires therapeutic intervention. This consists preferentially of chemotherapy of moderate intensity such as cyclophosphamide, vincristine and prednisone (COP) or prednimustine and mitoxantrone (PmM). In responding patients, maintenance therapy with interferon-α is currently being explored and may result in prolongation of disease-free and, possibly also, overall survival. In both high- and low-grade lymphomas, intensification of therapy by myeloablative chemotherapy or combined chemoradiotherapy followed by autologous bone marrow transplantation (ABMT) or peripheral stem cell transplantation provides a promising and potentially curative perspective. In addition, new cytostatic agents such as the purine analogues—fludarabine, chlorodeoxyadenosine and deoxycoformycin—enlarge the therapeutic spectrum. More experimental approaches consist of the application of immunotoxins or radioisotypes, coupled to monoclonal antibodies directed against lymphoma-specific antigens. Overall, the substantial advances that have been achieved in the understanding of the biology and pathogenesis of malignant lymphomas, as well as the current achievements of therapy and the new promising perspectives, justify the hope that curative therapy can soon be offered to an increasing proportion of patients with NHL.

Key words: non-Hodgkin's lymphoma, R.E.A.L. classification, prognostic factors, purine analogues, bone marrow transplantation, peripheral stem cell transplantation
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INTRODUCTION

NON-HODGKIN'S LYMPHOMAS (NHL) represent a heterogeneous group of disorders that differ in biology and natural history as well as in sensitivity to currently available chemotherapy and irradiation. In contrast to Hodgkin's disease (HD), the cellular basis of most types of NHL is well defined and represented by normal counterparts of lymphocyte development and differentiation. On this basis, the Kiel classification, developed by Lennert and coworkers, attempts to group NHL according to the corresponding stages of normal lymphopoiesis [1, 2]. Alternatively, the Working Formulation classifies NHL primarily according to its natural history and clinical course, discriminating between low-, intermediate- and high-grade lymphomas [3]. Since both classification systems delineate different subcat-

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egories, they are difficult to compare, and neither is completely satisfactory. While the Working Formulation relies almost exclusively on conventional morphology and does not include immunological and molecular techniques, the Kiel classification does not consider the extranodal lymphomas nor the heterogeneity of several lymphoma subtypes, especially follicular lymphomas. In an attempt to cope with these limitations and to develop an updated classification of NHL, an international panel of pathologists recently proposed a consensus classification which carries the working title of Revised European–American Lymphoma (R.E.A.L.) [4]. The clinical relevance of this system is currently under investigation. It is hoped that this proposal might provide a widely accepted basis which will facilitate the comparability of international studies and clinical evaluations. The three major classifications and their relationships are summarised in Table 1.

DETERMINANTS OF CLINICAL OUTCOME AND PROGNOSIS

Histology and morphology are not only the basis for the classification of lymphomas, but are also the major determinants for treatment outcome and prognosis. While high-grade lymphomas of all stages are generally treated with curative intention, final disease eradication cannot be achieved in low-grade lymphomas, with the possible exception of the small proportion of cases presenting at localised stages I and II [5–8]. Within the groups of low-, intermediate- and high-grade lymphomas, subgroups of patients with different prognoses can be further identified. In addition to stage and age, tumour bulk, the involvement of extranodal sites, performance status, serum lactate dehydrogenase and β_2-microglobulin levels, as well as other factors, have been shown to have prognostic implications [9–14]. Furthermore, an impaired recognition of lymphoma cells by the immune system, as indicated by the absence of the cell-surface expression of HLA-DR and β_2-microglobulin, may underlie the poor clinical outcome associated with these conditions [15, 16]. A joint evaluation of several major international multicentre trials led to the identification of five key parameters for prognosis: age, stage, serum lactate dehydrogenase level, performance status and number of extranodal sites. These determinants were used for the definition of an International Prognostic Index for high- and intermediate-grade lymphomas [17]. Via this index, four prognostic subgroups can be discriminated and future treatment strategies may be designed accordingly. Hence, more intensive approaches, such as myeloablative therapy with autologous bone marrow transplantation (ABMT) or even experimental regimens, may be initiated early in appropriately identified high risk patients, while a more conservative option may be adopted in cases with a low probability of relapse and disease-associated death. The International Prognostic Index may also be relevant for low-grade lymphomas, although further biological determinants may have to be considered in these disorders [18, 19]. Within any of the histological subtypes of NHL, a high tumour proliferation rate has been found to be associated with poor clinical outcome [20, 21]. Overall, these determinants may allow a more accurate estimation of the clinical course of NHL, and may provide the basis for risk-adapted stratifications of therapy.

PRINCIPLES OF CURRENT THERAPY

In spite of more refined prognostic factors, histology and stage still comprise the major determinants of therapy. As indicated previously, high-grade lymphomas are generally treated with curative intention, and combination chemotherapy comprises the basis of clinical management [6]. In localised stage I, and possibly also non-bulky stage II disease without B-symptoms or other adverse factors, radiotherapy alone may be sufficient [22]. Initial extensive diagnostic procedures including staging laparatomy are required, however, to ensure the limited extent of the disease. These procedures may put a greater burden on patients, who are often elderly, than alternatively applied chemotherapy of moderate intensity. Combination chemotherapy thus represents the preferred form of initial treatment in high-grade lymphomas of limited extent, and should consist of three to four cycles of CHOP (cyclophosphamide, hydroxy daunorubicine, vincristine and prednisone) immediately followed by involved field radiotherapy [23–26]. For more advanced disease (i.e. bulky stage II and stages III and IV), CHOP also remains the treatment of choice outside clinical investigations [6, 27]. The higher response rates initially

Table 1. The three major classifications of NHL

Kiel	Working formulation	R.E.A.L.
Low-grade lymphomas		
Lymphocytic	Small lymphocytic (A)	Lymphocytic
Lymphoplasmocytoid		Lymphoplasmocytoid
		Marginal zone
Centrocytic/centroblastic	Follicular small cleaved (B)	Follicle centre, follicular
(follicular, small)	Follicular mixed (C)	(small and mixed)
Intermediate-grade lymphomas		
Centrocytic/centroblastic	Follicular large (D)	Follicle centre, large
(follicular, large)		
Centrocytic	Diffuse small cleaved (E)	Mantle cell
Centrocytic/centroblastic	Diffuse mixed (F)	Follicle centre, diffuse (small)
(diffuse)	Diffuse large cell (G)	
High-grade lymphomas		
Immunoblastic	Immunoblastic, large cell (H)	Diffuse large B-cell
Centroblastic	Lymphoblastic, convoluted and	B-precursor large B-cell
	non-convoluted (I)	lymphoma-leukaemia
Lymphoblastic	Lymphoblastic, small-non-cleaved (J)	

reported for several second and third generation regimens proved not to be advantageous in a prospective randomised comparison, and were complicated by more pronounced side effects when compared with CHOP [28].

With currently available treatment programmes, complete remissions are achieved in 60–80% of adult patients with more advanced high-grade lymphomas, of whom 30–50% experience long-term remission and possible cure. A further improvement may result from attempts to increase treatment intensity by shortening the interval between treatment cycles, which appears feasible with the help of haematopoietic growth factors [29–31]. In addition, early intensification by myeloablative chemotherapy followed by ABMT or peripheral blood stem cell transplantation is currently being explored in defined high risk groups of patients as identified by adverse prognostic factors or a slow response to initial therapy [32–35].

Treatment of low grade NHL is mainly directed towards palliation, except for the small proportion (approximately 15–20%) of patients with limited stage I and II disease. In these cases, extended field or total nodal irradiation has been shown to result in long-lasting disease-free survival and possibly cure [36–39]. Subsequent adjuvant chemotherapy has not generally been found to further improve either disease-free or overall survival, and initial cytoreductive therapy followed by extended field irradiation is currently being investigated in a neo-adjuvant setting [40–43]. The majority of patients with low-grade lymphomas, however, present with more advanced disease for which a curative therapy is not yet available. Hence, a watch-and-wait approach still seems appropriate outside clinical investigations until the disease requires therapeutic intervention, indicated by the occurrence of haematopoietic impairment, B-symptoms, bulky disease or progressive lymphoma [8, 44, 45]. The type of chemotherapy to be initiated may comprise chlorambucil or cyclophosphamide either alone or together with corticosteroids, or combinations of moderate intensity such as COP (cyclophosphamide, vincristine and prednisone) or PmM (prednimustine and mitoxantrone) which produce higher rates of complete remission [8, 46, 47]. The early incorporation of anthracyclines or more aggressive treatment protocols have not proven beneficial, however, and should thus be reserved for salvage treatment [48–51]. A new approach may emerge from the incorporation of interferon-α into initial cytostatic therapy which has been shown to improve not only the remission rate, but potentially also disease-free and even overall survival [52, 53]. Currently, these data must be considered as preliminary, and require further follow-up before a final conclusion can be made. This reservation also applies to maintenance therapy with interferon-α after successful cytoreductive therapy, although a prolongation of the disease-free interval has been demonstrated by several (mostly still ongoing) controlled investigations [54–57]. Early data, however, suggest that the effect of interferon-α appears to be limited to the duration of interferon therapy, which is terminated after 12–18 months in most studies. The only trial with continuous interferon maintenance therapy carried out by the German Low Grade Lymphoma Study Group is still ongoing, and has not reached a statistically significant result [58].

FUTURE PERSPECTIVES

In both high- and low-grade lymphomas, intensification of therapy by myeloablative chemotherapy or combined chemo-radiotherapy followed by ABMT or peripheral stem cell transplantation provides a promising perspective. These approaches have so far been explored mainly in relapsed or refractory lymphomas, and have demonstrated a significant, although limited, potential for cure [34, 59–61]. Hence, they are currently being investigated at earlier stages of therapy, and the results of these ongoing studies are anxiously awaited. The use of peripheral blood stem cells, in particular, has substantially facilitated the applicability of myeloablative treatment programmes, not only by providing easy access to haematopoietic progenitor cells, but even more by allowing a rapid reconstitution of haematopoiesis. Correspondingly, the fatality rates have been reduced to below 2–3% in most centres, and this type of therapy has now become more accessible to older patients. This advance may be of special relevance for low-grade lymphomas that occur in older patients and that have a high sensitivity to radiotherapy. Hence, consolidation therapy with total body irradiation and high-dose cyclophosphamide followed by blood stem cell reinfusion comprises a promising and potentially curative option for patients with advanced low grade lymphomas.

Future perspectives also arise from new cytostatic agents—purine analogues in particular (fludarabine, 2-chlorodeoxyadenosine and deoxycoformycin). While the latter exerts a high activity in hairy cell leukaemia and is less effective in other lymphoid malignancies, fludarabine and 2-chlorodeoxyadenosine have revealed a significant efficacy in low-grade lymphomas of the follicular subtype [62]. Fludarabine has been investigated most extensively in relapsed and refractory cases with response rates ranging from 37 to 55% [63–65]. A further increase in activity could be achieved by the combination of fludarabine with mitoxantrone and dexamethasone, which produced remissions in up to 85% of heavily pretreated patients [66]. Hence, these agents are currently being explored at earlier stages of lymphoma therapy, and will certainly enlarge the armamentarium of currently available antilymphoma agents.

A still more experimental approach consists of the application of immunotoxins or radioisotopes coupled to monoclonal antibodies that are directed against specific lymphoma antigens. In two recent studies, response rates of more than 80% were obtained in relapsed B-cell lymphomas by administration of the anti-CD20 pan-B-cell monoclonal antibody conjugated to the radioisotope ^{131}I [67, 68]. Although the associated myelosuppression required the support of autologous bone marrow reinfusion, the high remission rate and especially the relatively long duration of response to these treatments hold much promise for this approach.

CONCLUSION

Substantial advances have been made in unravelling and understanding the biology and pathogenesis of malignant lymphomas through the use of modern molecular, immunological and cytogenetic techniques. They provide a better basis for the classification of these disorders, but also for a more appropriate design of therapy. Based on current achievements of treatment and new promising perspectives, there is justified hope that curative therapy can soon be offered to an increasing proportion of patients with malignant lymphomas.

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